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BRIEF REPORT

A high prevalence of BRCA1 mutations among breast cancer patients from the Bahamas

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Abstract The Bahamas is a group of islands in the Caribbean with a high incidence of early onset breast cancer. In isolated populations, the identification of founder mutations in cancer predisposing genes may facilitate genetic testing and counseling. To date, six distinct BRCA1 mutations have been found in patients from cancer families from the Bahamas. The frequencies of these mutant alleles have not been measured in a large series of unselected breast cancer patients from Bahamas. We studied 214 Bahamian women with invasive breast cancer, unselected for age or family history of cancer. All patients were screened for six mutations in the BRCA1 gene that have previously been reported in cancer patients from the Bahamas. A mutation was identified in 49 of the 214 breast cancer patients (23%). The mutation frequency was particularly high in women diagnosed before age 50 (33%) in women with a first-degree relative with breast or ovarian cancer (41%) and in women with bilateral breast cancer (58%). Approximately 23% of unselected cases of breast cancer in the Bahamian population are attributable to a founder mutation in the BRCA1 gene—this is the highest reported mutation prevalence for any country studied to date. Genetic testing for these mutations is advisable for all women diagnosed with breast cancer in the Bahamas.

Keywords Breast cancer · BRCA1 · Hereditary · Bahamas

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Introduction

In Canada and the United States, from 3 to 5% of all breast cancer cases are due to a mutation in one of two cancer susceptibility genes, BRCA1 and BRCA2 [1–3]. The prevalence of mutations among cancer cases may be higher than this in other countries for a number of reasons, including a low background rate of (non-hereditary) cancer and a relatively high proportion of young women in the population and the presence of one or more founder mutations. Populations with a high frequency of BRCA mutations among breast cancer patients due to founder effects include Ashkenazi Jews, French-Canadians, Poles, and Lithuanians [4–7].

The genetic composition of a given population may be distinct from that of neighboring populations due to historical patterns of migration and relative reproductive isolation. These factors may be particularly relevant for island populations with a small number of founders.

Several prevalence surveys of BRCA mutations have been conducted among women of African or African-American descent [8–15]. These studies show that the spectrum of mutations among Africans is different from that of white women, but in most studies, the overall prevalence of mutations is comparable. However, most

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previous studies have been based on cases which have been selected for age or family history. In order to estimate accurately the hereditary burden of breast cancer, it is ideal to study unselected cancer patients.

The Bahamas is an island group in the Caribbean with a total population of approximately 300,000, most of whom are of African origin. Based on a previous study from our group [16], the average age of onset of breast cancer in the Bahamas is 42 years and 48% of cases are diagnosed under the age of 50, compared to 23% in white women and 32% in women of African descent in the United States [17]. Early onset breast cancer is a characteristic of hereditary breast cancer, including cases that are associated with mutations in BRCA1 and BRCA2. It is not clear to what extent the high proportion of young onset breast cancers in the Bahamian population may be explained by hereditary factors.

In an earlier study, we postulated that BRCA1 and BRCA2 mutations might be a significant cause of breast cancer in the Bahamas [18]. We studied 19 patients who were born in the Bahamas and who presented for treatment in Miami. The 19 patients were studied because they had ovarian cancer at any age ($n = 3$) or invasive breast cancer diagnosed at or before age 50 ($n = 15$) or breast cancer diagnosed after age 50 and a family member with breast cancer ($n = 2$) (one patient had both breast and ovarian cancer). DNA was analyzed for mutations in BRCA1 and BRCA2 by full sequence analysis and a five large rearrangement panel (Myriad Genetics). Nine of 19 (47%) of the study subjects had a deleterious mutation in BRCA1. The 4730insG mutation was seen in four unrelated patients and the IVS13+1G>A mutation was seen in three unrelated patients. Two mutations (IVS16+6T>C and M1775R) were found in single families. No BRCA2 mutation was seen.

Two other mutations have been identified in Bahamian breast cancer patients. The first (943ins10) was described in 1999 in a family of Bahamian descent living in Miami [19]. The second (185delAG) was reported to us by a Bahamian resident who had a family history of early onset breast cancer who had been tested previously. We sought to estimate the frequency of these six mutations in unselected Bahamian women with breast cancer.

Methods

Breast cancer patients were recruited from public and private clinics in Freeport, on the island of Grand Bahama, in Nassau on the island of New Providence and from several outlying islands between September 2008 and January 2010. Women were eligible for this study if they had been diagnosed with invasive primary breast cancer at any age, in any year and if at least one parent was born in the Bahamas. Patients may have had first primary or second primary breast cancer. Initially, patients were offered participation on the study through their oncologists. There was broad general acceptance of this study in The Bahamas and referrals came in through the local cancer societies. In addition, media attention brought the study to the attention of many patients who volunteered for the study. Subject accrual centers were set up at the Princess Margaret Hospital Oncology Centre, at the Cancer Society in Nassau, at the Cancer Association in Freeport, at Cancer Societies in Eleuthera and Abaco, at the Government Clinic of St George's Cay and at a private home in Harbor Island. In addition, breast cancer patients who were born in the Bahamas were eligible for the study in Miami, at the University of Miami, Jackson Memorial Hospital and the Mount Sinai Cancer Center. All women provided written consent to participate in the study. The study protocol was approved by the ethics review board of the University of Miami, Jackson Memorial Hospital, Mount Sinai Cancer Center, Princess Margaret Hospital, Doctors Hospital, and the Bahamian Ministry of Health.

In total, 214 women from 193 different families, agreed to participate. A saliva sample was taken from each of these women and a medical and family history was taken by interview. The family history asked about cancer diagnoses in first and second degree relatives (Table 1).

Mutation analysis

Saliva was collected using the Oragene®•DNA sample collection kit (OG-250 format, DNA Genotek) and extracted following the manufacturer's instructions. DNA was then quantified using the NanoDrop ND-1000 Spectrophotometer.

All samples were screened for five BRCA1 mutations previously seen among the African-American population (Table 2). Three mutations, IVS13+1G>A [20], IVS16+6T>C [21], and 5443T>G [22, 23] were detected using an amplification refractory mutation system (ARMS) assay [24]. Briefly, two allele-specific amplicons are generated using two pairs of primers. One pair produces an amplicon representing the wildtype allele, and the other corresponding to the mutant allele. The two allele-specific amplicons differ in length, allowing discrimination by gel electrophoresis possible. The exon11 943ins10 [19] mutation was detected using flanking primers, and run on a 2.5% agarose gel. The final mutation, exon15 4730insG [20] was amplified with a Cy5 labeled forward primer, and run on a 6% Bis/Acrylamide gel. Detection for this mutation was possible using direct fluorescence on a Storm 860 Molecular Imager (General Electric). All mutations detected by these screening methods were confirmed by direct sequencing [BigDye Terminator v3.1 Cycle Sequencing Kit, and 3130XL

Table 1 Characteristics of the 214 breast cancer patients in the study

Characteristic	
Age mean (range)	51.8 (26–83)
Number of breast cancers in relatives (proband excluded)	
0	81
1	56
2	32
3	18
4	9
5+	18
Number of ovarian cancers in relatives	
0	188
1	22
2+	4
Year of diagnosis	
<2000	63
2001	8
2002	10
2003	10
2004	10
2005	13
2006	22
2007	38
2008	30
2009	9
2010	1
Unilateral	195
Bilateral	19

Table 2 Description of mutations identified in the study

Mutation	Frequency
BRCA1 Exon 21 T5443G	5
BRCA1 Exon 15 4730insG	6
BRCA1 IVS13+1G>A	30
BRCA1 IVS16+6T>C	3
BRCA1 exon11 943ins10	3
BRCA1 exon2 185delAG	2

Genetic Analyzer (Applied BioSystems)] according to manufacturer's instructions. Primers used for all assays and sequences are available upon request. The 185delAG mutation is found among the Jewish population and the technique is previously described [25].

Statistical analysis

The prevalence of all mutations combined was derived from the ratio of the number of individuals observed with a mutation and the total number of women tested. The prevalence figures were estimated for individual mutations and for subgroups defined by age of diagnosis and family history of cancer.

Results

A BRCA1 founder mutation was identified in 49 of the 214 patients (22.9%). The mutation prevalence was higher for women diagnosed before age 40 (45.3%; 29 of 64) than for women diagnosed from age 40 to 59 (14.4%; 19 of 132) (Table 3). One mutation was identified among 20 women diagnosed after age 59. The mean age of diagnosis in the entire study group was 45.4 years. The mean age of diagnosis was 38.2 years for the 49 hereditary cases and was 47.5 years for the non-hereditary (mutation-negative) cases. Of the total of 49 mutations, 46 (93.9%) were identified in women diagnosed before age 50.

There were 19 women with bilateral cancer (either synchronous or with a past history of breast cancer). Among these, 11 mutations were found (57.9%).

One hundred eleven (51.9%) of patients had at least one-first- or second-degree relative with breast or ovarian cancer. Among these, the mutation prevalence was 34.2%. Of the 49 women with a mutation, 36 had a first- or second-degree relative with breast cancer (73.5%) and eight had a first- or second-degree relative with ovarian cancer (16.3%). 11 of the 49 women with a mutation had no first- or second-degree relative with breast or ovarian cancer (22%). Of the 103 women with no first- or second-degree relative with breast or ovarian cancer, 11 had a mutation (10.7%).

Discussion

In this study, we estimate the prevalence of six founder mutations in the BRCA1 gene to be 22.9% in 214 unselected Bahamian breast cancer patients. To our knowledge, this is the highest prevalence of BRCA1 mutations for any

Table 3 Prevalence of mutations by age of diagnosis

Age group	Number of subjects	Number of mutations	Mutation prevalence (%)
20–29	13	8	61.5
30–39	51	21	41.2
40–49	77	17	22.1
50–59	53	2	3.8
60+	20	1	5.0

population or for any country studied to date. Among women in the Bahamas diagnosed with breast cancer under the age of 40, almost one-half were attributable to mutations in BRCA1. This may explain, to some degree, the early average age of diagnosis of breast cancer in the Bahamas. The reason for the high mutation rate may lie in the historical patterns of immigration to the islands. The indigenous population of the Bahamas was relocated as slave labor to Hispaniola by the Spaniards. Certain islands of the Bahamas were populated in the 1600s by a small group of British settlers. After the American revolution in 1776, Loyalists settled in the Bahamas with their black slaves. After the abolition of slavery by the British in 1833, ships of African slaves were diverted to the Bahamas. Therefore, the black residents of the Bahamas represent a genetic subsample of the original sample of West Africans who were brought to the United States.

The immigration history of the Bahamas may also illuminate the origin of the six specific mutations. Five of the six founder mutations have been reported previously in patients of African descent. Four of these mutations (IVS13+1G>A, M1775R [5443T>G], 943ins10, and IVS16+6T>C) have been reported by Myriad Genetics as recurrent mutations in patients with African ancestry [9]. Each of these mutations was present in over 2% of the 1767 African-American patients tested by Myriad Genetics Lab, but specific ancestral origins are not provided [9].

The most common mutation in our study (IVS13+1G>A) represented 61.2% of the total number of mutations. This splice-site mutation has been listed 21 times in the Breast Cancer Information Core database [20] in individuals of Western European, African [8], Latin/Caribbean, or Native American backgrounds. Pal et al. [26] reported this mutation in 1 of 10 high risk breast/ovarian families of African-American background.

We observed the 943ins10 mutation in three patients. Although relatively rare in our sample, this is the most commonly reported African founder [8, 9]. The mutation has been reported in a family of Bahamian descent living in Florida [19], a French family from the Ivory Coast [27], and in many African-Americans families [8, 9, 11, 12, 19, 26, 28]. The mutation was recently reported in a Mexican woman [29] and in three other patients of Latin American/Caribbean background in the BIC database [20].

The M1775R mutation is one of the first reported missense mutations in BRCA1 [22, 23]. In the BIC database, it has been reported 31 times in women of African, Latin/Caribbean, Native American, and West European origins [20].

The IVS16+6T>C mutation is also one of the most commonly recurring mutations in the African-American population [9] and is reported in patients from multiple ethnic backgrounds in the BIC database [20]. Palma et al. reported this mutation in 2 of 16 high risk African-American families [30].

4730insG has not previously been described in families in the literature, but has been listed in the BIC database on four occasions, with ethnicity reported as African, not further specified [20].

We identified the 185delAG mutation in two unrelated white breast cancer patients from the island of Abaco. They did not identify themselves as Jewish. This is the most common founder mutation in the Ashkenazi Jewish population, but has also been reported on occasion in other ethnic groups [9, 11, 12, 29, 31] including individuals from the United Kingdom that do not share the same Ashkenazi Jewish haplotype [32].

In our study, 29 of 64 patients diagnosed with breast cancer under age 40 were found to have one of the six BRCA1 mutations tested (45.3%). In comparison, a BRCA mutation was found in 27% of Jewish women diagnosed under age 40 [4], in 13% of French-Canadians [7], and in 9% of Polish women tested [33]. In Nigeria, Gao et al. [13] studied 70 patients diagnosed with breast cancer under age 40 and found three with deleterious mutations (4%).

Few studies report rates of BRCA mutations in the Caribbean or South American populations with high African backgrounds. Rodriguez et al. [34] reported a low frequency (2.6%) of mutations in unselected breast cancer patients in Cuba. Similarly in Brazil, only 2.3% of 402 breast cancer cases from both public and private hospitals were found to have a BRCA1 or BRCA2 mutation [35].

If mutation testing were restricted to familial cases; then 22% of the women in our study with mutations would be missed. Based on these results, it is reasonable to consider testing all Bahamian women with breast cancer, regardless of age. It is expected that the founder mutation panel will identify the majority of mutations in the population and full gene screening can be reserved for women with extended family histories who test negative for these mutations.

There are several limitations to our study. We restricted our study to six mutations. It is possible that additional mutations exist in the Bahamas. Complete sequence analysis and MLPA in the patients diagnosed at young ages, or with strong histories are underway to fully characterize the spectrum of BRCA1 and BRCA related breast cancer in the Bahamas.

It is possible that our sample was biased toward early onset breast cancer or familial cases due to self-selection. We did not test all incident cases of breast cancer diagnosed during a specific time period. Rather, we studied prevalent cases that were identified by Bahamian oncologists, the cancer Societies, the patient advocate groups, and self-referrals. Those with a positive family history may have been more motivated to attend. While Nassau is the most metropolitan of the islands, trips were made to reach

additional populations at five islands, several with unique and reproductively preserved ethnic groups.

Our study included patients who described a personal history of breast cancer. It is possible that some of these patients may, in fact, have had DCIS or a benign breast condition and not had invasive breast cancer. If so, we may have under-estimated the hereditary fraction of cancers among invasive cancers.

In conclusion, we identified one of six founder mutations in BRCA1 in 23% of Bahamian women with breast cancer. This is the highest prevalence reported among any population studied to date. It is feasible to create a rapid and inexpensive multiplex assay to test for these six mutations in unselected women with breast cancer from the Bahamas. This approach should be able to identify the majority of mutations in BRCA1 in this population.

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Conflict of interest None.

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